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Do sex differences in chronic disease underpin the sex-frailty paradox?

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ABSTRACT

The 'male-female health-survival paradox' is a well-described clinical phenomenon. More recently, it has been conceptualized as a 'sex-frailty paradox': females may be considered to be more frail (because they have poorer health status) but also less frail (because they are less vulnerable to death) than males of the same age. Here, we review potential biological, behavioral and social mechanisms underpinning sex differences in morbidity, mortality and frailty before considering the question at the center of the sex paradox – why is it that females are able to tolerate poor health better than males? We explore, in detail, a frequently cited explanation for the sex paradox that centers on sex differences in chronic disease and conclude by presenting a new approach to this old hypothesis.

1. Introduction

The 'male-female health-survival paradox' is a well-described phenomenon in modern human populations (Oksuzyan et al., 2008). Even though average human life expectancy has changed over time, historical records indicate that females have lived longer than males since at least the 18th century (Alberts et al., 2014; Thorslund et al., 2013). However, this survival advantage has not been accompanied by health advantages, with females burdened by chronic disease and disability to a greater extent than their male counterparts (Oksuzyan et al., 2008).

Several biological, behavioral and social explanations for the sex paradox have been proposed and tested in the literature. However, exploring sex differences in health is challenging, as there are many different, yet inter-related, measures available to researchers. In more recent times, 'frailty' has emerged as a useful construct to evaluate health status. Frailty is a multidimensional measure of health, which links morbidity with adverse outcomes (including, but not limited to, death). Frailty, therefore, captures the relationship central to the male-female health-survival paradox. Here, we review sex differences in frailty and summarize pathophysiological hypotheses for the sex paradox before exploring, in detail, a frequently cited theory regarding sex differences in chronic disease. We conclude by presenting a new approach to this old hypothesis.

2. Sex differences in frailty

Frailty studies show that not only is the prevalence of frailty higher in females than in males, females also experience greater levels of frailty than males of the same age (Collard et al., 2012; Shamliyan et al., 2013; Gordon et al., 2017). A recent meta-analysis of data from seven large studies of community-dwelling older adults demonstrated that females tolerate their frailty better than males, as demonstrated by a lower mortality rate at any given age or level of frailty (Gordon et al., 2017). Put another way, when compared with males of the same age, females may be considered to be more frail (because they have poorer health status) but also less frail (because they are less vulnerable to death). This 'sex-frailty paradox' is, therefore, another conceptualization of the male-female health-survival paradox.

2.1. Biological, behavioral and social explanations for the sex paradox

Biological, behavioral and social factors that contribute to sex differences in morbidity and mortality have been a focus of research over the last few decades. Frequently cited hypotheses are summarized in Table 1. More recently, however, attention has turned to the pathophysiology of sex differences in frailty.

Many of the same biological factors are thought to contribute to the sex-frailty gap. For example, chronic inflammation has been identified as a key factor contributing to the development of frailty and some early findings suggest that inflammation may play a more critical role in the pathophysiology of frailty in females than in males (Gale et al., 2013). Sex differences in diet, gut microbiome and adiposity have all been implicated in the relationship between sex, chronic inflammation and frailty (Gordon and Hubbard, 2018). Estrogen and testosterone may contribute to sex differences in frailty by modulating inflammation (Fougere et al., 2017), as well as having direct effects on other tissues,

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Table 1
Summary of hypotheses: biological, behavioral and social factors underpinning sex differences in mortality and morbidity.

		Why do females live longer than males?	Why do females have poorer health than males?
Biological Factors	Genetic	The presence of two X-chromosomes may confer a survival and/or aging advantage due to selective chromosome inactivation (Eskes and Haanen, 2007). Longer telomeres and slower shortening processes may contribute to female longevity (Haapanen et al., 2018).	
	Hormonal	The favorable effect of estrogens on the vasculature and lipid profile of premenopausal females may be a key factor contributing to the later onset and lower burden of atherosclerosis in females (Eskes and Haanen, 2007). Testosterone may reduce the robustness of the male immunological system (Gubbels Bupp, 2015).	The increased risk of autoimmunity in females may be attributed to the immunological effects of estrogens (Gubbels Bupp, 2015).
	Immunological	Testosterone curbs innate and adaptive immune responses exposing males to risk of life-threatening infections (Gubbels Bupp, 2015; Owens, 2002). Males may experience immunosenescence to a greater extent and at a more accelerated rate than females, which may have implications for aging and survival (Gubbels Bupp, 2015).	Chronic inflammation may contribute to aging (e.g., sarcopenia and cognitive impairment) in females to a greater extent than males (Canon and Crimmins, 2011). Abdominal adiposity, which accumulates to a greater extent in older females than males, may contribute to sex differences in chronic inflammation (Hubbard et al., 2010).
	Burden of chronic disease and disability	Males appear to be more likely than females to acquire 'lethal' conditions, such as stroke and myocardial infarction (Avedano and Mackenbach, 2008; Crimmins et al., 2010).	Females appear to be more likely to acquire 'disabling' conditions, such as, obesity, arthritis, cataracts and depression (Avedano and Mackenbach, 2008; Crimmins et al., 2010). Higher prevalence of depression in females may compound the negative, 'disabling' effects of other conditions (Verbrugge, 1985; Whitson et al., 2010; Newman and Brach, 2001). Females self-report and demonstrate more physical and functional impairment than males (Avedano and Mackenbach, 2008; Crimmins et al., 2010; Merrill et al., 1997; Gorman and Read, 2006a).
Behavioral and Social Factors	Risk-related activities	Males engage more frequently in high-risk behaviors, such as cigarette smoking, alcohol consumption, illicit drug use and unsafe driving, which may contribute to increased prevalence of 'lethal' co-morbidities and mortality (Oksuzyan et al., 2008).	
	Illness perception		Females may be more sensitive to physical changes or discomforts (Verbrugge, 1985).
	Health reporting behavior		Females may be more willing than males to describe and discuss physical and psychological symptoms leading to higher rates of diagnosis (Verbrugge, 1985). Females may be more willing to identify and report minor and major health issues to others (Verbrugge, 1985).
	Healthcare utilization	Females access healthcare more than males, which may play a key role in preventative health care and early intervention. In turn, this may contribute to greater survival (Oksuzyan et al., 2008; Verbrugge, 1985).	
	Gender roles	Expectations and responsibilities associated with gender roles may contribute to the willingness (and ability) of the sexes to adopt the 'sick role', seek help and access healthcare. This in turn may influence morbidity and mortality (Verbrugge, 1985; Hibberd and Pope, 1986).	

such as bone, muscle and vasculature (Carcaillon et al., 2012; Gubbels Bupp, 2015). At this stage, it is unclear whether sex differences in other immunological processes, such as immunosenescence, contribute to sex differences in frailty. Current evidence suggests that telomere length is not associated with frailty (Yu et al., 2015). However, relationships between sex, frailty and single nucleotide polymorphisms in several genes (including those impacting mitochondrial energy generation, insulin secretion and reactive oxygen species generation) have been recently identified (Kim et al., 2016).

Most frailty studies have been conducted in humans, yet biological hypotheses for sex differences in human longevity draw on observations and experiments conducted in human and non-human species (Austad, 2006). Animal, particularly murine, models of frailty are evolving and there is a growing interest in the pathophysiology of sex differences. For example, Kane and colleagues (Kane et al., 2018) recently demonstrated that the association between frailty and inflammatory cytokines in aging mice differed in a sex-specific way. It is anticipated that animal models will help to elucidate the biological factors that underpin sex differences in frailty in aging men and women.

Behavioral and social factors may also be important mediators of sex differences in frailty. For example, sex differences in health reporting behavior may contribute to the sex-frailty gap. In a study of 4961 Irish community-dwellers, males demonstrated higher frailty scores than females when the frailty measure comprised of performance- or test-based items, whereas females demonstrated higher frailty scores than males when the frailty measure comprised of self-report items or a combination of self-report, performance- and test-based items (Theou et al., 2015). With respect to risk-related activities, cigarette smoking has been associated with baseline and incident frailty in both sexes (Hubbard et al., 2009; Kojima et al., 2015). However, it is unclear whether smoking behavior significantly affects the sex-frailty gap. Certainly, it is hard to imagine that past or current smoking (which is more prevalent in males) would confer a 'frailty advantage' to the male sex. The relationship between alcohol and frailty seems to be even more complex, with current evidence indicating beneficial effects of moderate alcohol intake and detrimental effects of abstinence (and possibly heavy alcohol intake) on prevalent and incident frailty (Shah et al., 2018; Kojima et al., 2017). At this stage, evidence for significant sex differences in this non-linear relationship is limited. Social support, marital status and socioeconomic factors (such as education level, wealth and income) have all been associated with frailty in both sexes (Szanton et al., 2010; Andrew et al., 2008; Woo et al., 2005; Trevisan

et al., 2016). However, studies suggest that these social assets and deficits may affect male and female frailty in different ways (Andrew et al., 2008; Woo et al., 2005).

Overall, a review of the literature reveals that there are many potential biological, behavioral and social explanations for sex differences in morbidity, mortality and frailty. However, these explanations, when considered in isolation, do not address the question central to the paradox – why is it that females are able to tolerate poor health better than males? That is, why do females have a lower risk of death despite being more frail?

The sex paradox likely reflects a complex interplay of many, if not all, of the biological, behavioral and social factors outlined so far. However, other hypotheses do exist. For example, it has been proposed that females have greater physiological reserve than males (Hubbard and Rockwood, 2011). This would enable them to acquire more deficits in multiple organ systems before succumbing to death. Or, perhaps females have more 'health assets' than males, which provide resilience in the face of increasing frailty. Or, maybe the sex paradox transpires because health measures (including frailty measures) do not adequately capture health deficits in males (Theou et al., 2015; Howlett et al., 2014). That is, 'sub-clinical' deficits (which may be more readily identified on laboratory- or test-based measures) may be particularly informative when considering the health and survival of males. The literature indicates, however, that the leading (or at least, the most enduring) hypothesis regarding the sex paradox is the 'chronic disease hypothesis' (Verburgge, 1985).

3. The 'chronic disease hypothesis'

In the 1980s, Verbrugge (Verbrugge, 1985) proposed that females experience more chronic conditions than males, but conditions are typically 'not serious' or 'non-life-threatening', resulting in high morbidity and low mortality. Males, on the other hand, experience more 'life-threatening' chronic conditions, resulting in high mortality. Over the last 30 years, this hypothesis has been periodically re-visited in studies of community-dwelling adults (Avedano and Mackenbach, 2008; Crimmins et al., 2010; Newman and Brach, 2001; Verbrugge, 1985; Case and Paxson, 2005). Here, we review the evidence.

3.1. Sex differences in multimorbidity

It has been proposed that excess female morbidity can be attributed, in part, to sex differences in the number of chronic conditions experienced by older adults (Verbrugge, 1984). However, studies of multimorbidity prevalence (i.e., the presence of two or more chronic conditions) and burden (i.e., the total count of chronic conditions) have yielded inconsistent results regarding significant sex differences (Abad-Diez et al., 2014; Kirchberger et al., 2012; Schafer et al., 2012). In some studies, sex differences in multimorbidity may have been overestimated due to significant differences in life expectancy of males and females. In others, multimorbidity, particularly in females, may have been underestimated due to the limited spectrum of diagnoses. That is, many common conditions that significantly impact health status via troubling symptoms or functional impairment are thought to be more prevalent in females and are not well captured in epidemiological studies that tend to focus on more 'fatal' conditions (Verbrugge, 1985). Sex differences in multimorbidity are, therefore, highly sensitive to research methodology. As a result, a count of medical conditions, on its own, is unlikely to contribute greatly to our understanding of the sex paradox.

3.2. Sex differences in chronic disease prevalence

Another approach in the literature has been to explore this hypothesis by comparing the prevalence of chronic conditions in male and female community-dwellers (Crimmins et al., 2010; Case and Paxson, 2005; Verbrugge, 1984; Ferrucci et al., 2003). For example, a study of 50,000 non-institutionalized older adults from Europe, United Kingdom and North America reported greater female prevalence of hypertension, arthritis and depression, and greater male prevalence of heart disease, which lead them to conclude that females had a higher prevalence of 'non-life-threatening' disease, whereas males had a higher prevalence of 'life-threatening' disease (Crimmins et al., 2010).

This theory is appealing from a pathophysiological point of view. For example, estrogens are thought to have a favorable effect on the vasculature of premenopausal females, which may explain the earlier onset and higher burden of atherosclerosis in males (Gubbels Bupp, 2015; Eskes and Haanen, 2007). Whilst the incidence of coronary artery disease in postmenopausal females approaches that of males, the higher prevalence of atherosclerotic disease in males when compared with females may explain why males face a higher risk of mortality despite a lower burden of clinical frailty. Marked redistribution of adipose tissue to the abdomen in postmenopausal females results in higher prevalence rates of obesity in older females than males (Perissinotto et al., 2002) and most would agree that obesity and its sequelae (particularly osteoarthritis) impact significantly on function and mobility.

Whilst cardiovascular disease and osteoarthritis are often cited as key conditions contributing to the male-female morbidity-mortality gap (Verbrugge, 1985; Gorman and Read, 2006b), a review of the literature demonstrated that sex differences in the prevalence of common medical conditions have not been as clear as we may have been lead to believe (see Table 2).

Substantial differences in sample size, participant characteristics (such as age and ethnicity) and statistical analyses may explain some of these inconsistencies. For example, in some studies, adults aged 65 years (Verbrugge, 1984) were considered as one group even though it is likely that sex differences in chronic medical conditions continue to evolve with increasing age (Gorman and Read, 2006b). Sex differences in disease prevalence are also likely to vary between countries and cultures due to social and behavioral differences that impact male and female health (Crimmins et al., 2010). Some studies drew conclusions from raw prevalence rates and others used statistical techniques to compare proportions or develop regression models (with medical conditions as the dependent variables). In regression analyses, covariates also differed, potentially adding to inconsistencies.

Whilst the majority of studies examined prevalence rates of individual conditions, two studies explored sex differences in the count of 'serious' or 'life-threatening' conditions in older adults and yielded conflicting results (Gorman and Read, 2006b; Liang et al., 2003). Both studies included stroke, hypertension, diabetes and heart disease in their list of conditions, but the study that included cancer and emphysema as additional conditions found a higher risk of 'life-threatening' conditions in males. There were, however, other between-study differences, such as differences in the management of confounding factors, choice of dependent variables in statistical analyses and participant characteristics, that contributed to the discordant results.

Although some studies used medical records (e.g., from primary care) to obtain medical diagnoses, most relied on self-report data. There is evidence of reasonable agreement between self-report and medical records (Okura et al., 2004), but accuracy of self-report may be affected by factors such as disease severity and acuity (Bergmann et al., 1998). In studies using self-report data, conclusions regarding sex differences in medical conditions depend upon whether males and females self-report their conditions in the same way. Whilst it is hypothesized that females over-report and males under-report health problems, the literature is conflicting (Oksuzyan et al., 2008; Macintyre et al., 1999). Utilizing multiple sources of information to determine medical diagnoses (rather than purely self-report methods) should be considered in future studies to reduce potential reporting bias.

Issues regarding the selection and categorization of medical conditions also impact the usefulness of study findings. Firstly, the medical conditions under investigation varied greatly between studies and very few studies outlined their methodology in detail. Some extracted the

Table 2
Sex differences in the prevalence of chronic medical conditions in older adults.

More prevalent in males	More prevalent in females	Equal prevalence
Hearing impairment (Whitson et al., 2010; Case and Paxson, 2005; Verbrugge, 1984; Shi et al., 2014)		
Hernia (Verbrugge, 1984)		
Cardiovascular disease(Case and Paxson, 2005)		Cardiac disease (Kingston et al., 2014)
		Congestive cardiac failure (Ferrucci et al., 2003)
Ischemic heart disease (Ferrucci et al., 2003)		Coronary artery disease (Shi et al., 2014)
Coronary artery disease (Whitson et al., 2010)		
Congestive cardiac failure (Whitson et al., 2010)		
Heart disease (Crimmins et al., 2010; Verbrugge, 1984)		
Heart trouble (Macintyre et al., 1996)		
Peripheral vascular disease (Ferrucci et al., 2003)		
Claudication (Whitson et al., 2010)		
Cerebrovascular disease (Kingston et al., 2014)		Stroke (Crimmins et al., 2010; Ferrucci et al., 2003; Macintyre et al., 1996)
Stroke (Whitson et al., 2010; Shi et al., 2014)		
Gastrointestinal diseases (Ferrucci et al., 2003; Macintyre et al., 1996)		Liver disease (Macintyre et al., 1996)
Diabetes mellitus (Whitson et al., 2010)	Diabetes mellitus (Verbrugge, 1984)	Diabetes mellitus (Crimmins et al., 2010; Case and Paxson, 2005; Ferrucci et al., 2003; Macintyre et al., 1996; Kingston et al., 2014)
Chronic obstructive pulmonary disease (COPD) (Case and Paxson, 2005; Ferrucci et al., 2003)	Bronchitis (Whitson et al., 2010)	Respiratory disease (Crimmins et al., 2010; Kingston et al., 2014)
		Asthma (Case and Paxson, 2005; Macintyre et al., 1996)
Emphysema (Whitson et al., 2010)		Bronchitis (Macintyre et al., 1996)
	Arthritis (Whitson et al., 2010; Case and Paxson, 2005; Verbrugge, 1984; Kingston et al., 2014)	Osteoarthritis (Shi et al., 2014)
	Osteoarthritis (Crimmins et al., 2010; Ferrucci et al., 2003)	
	Arthritis/rheumatism (Macintyre et al., 1996)	
	Hypertension (Crimmins et al., 2010; Case and Paxson, 2005; Verbrugge, 1984; Macintyre et al., 1996; Kingston et al., 2014)	Hypertension (Shi et al., 2014)
	Vision impairment (Case and Paxson, 2005; Verbrugge, 1984)	Glaucoma (Shi et al., 2014)
		Cataracts (Shi et al., 2014)
	Varicose veins (Verbrugge, 1984; Macintyre et al., 1996)	Phlebopathies (Ferrucci et al., 2003)
	Depression (Crimmins et al., 2010; Whitson et al., 2010; Case and Paxson, 2005; Ferrucci et al., 2003; Macintyre et al., 1996)	
	Cognitive impairment (Kingston et al., 2014)	
	Dementia (Ferrucci et al., 2003)	
	Hip fracture (Ferrucci et al., 2003)	
	Fracture (Whitson et al., 2010; Shi et al., 2014)	
	Thyroid disease (Shi et al., 2014)	
	Urinary incontinence (Shi et al., 2014)	
	Constipation (Verbrugge, 1984)	
	Headache (Case and Paxson, 2005; Macintyre et al., 1996)	
	Obesity (Whitson et al., 2010)	
		Cancer (Ferrucci et al., 2003; Kingston et al., 2014)
		Parkinson's disease (Ferrucci et al., 2003)
		Epilepsy (Macintyre et al., 1996)

most prevalent conditions from a sample population and then compared the sexes (Verbrugge, 1985; Case and Paxson, 2005), whereas others compared the male and female prevalence of a pre-determined list of conditions (Avedano and Mackenbach, 2008; Crimmins et al., 2010). Some studies used acute illnesses to represent chronic medical conditions, such as 'hip fracture' for osteoporosis and 'stroke' for cerebrovascular disease, which may have lead to an underestimation of prevalence rates (Ferrucci et al., 2003). Studies also varied in the way they categorized conditions. For example, some studies examined the prevalence of 'heart disease' (Crimmins et al., 2010) whereas others delineated the prevalence of specific conditions, such as 'ischemic heart disease and 'congestive cardiac failure' (Ferrucci et al., 2003). Not only does this affect the ability to integrate results across studies, but the way in which conditions were classified may have impacted the results regarding sex differences. For example, in a study where females and males had similar prevalence of cardiovascular disease overall, the cardiovascular conditions found to be more prevalent in females (such as hypertension and peripheral vascular disease) were considered to carry a lower risk of mortality than the cardiovascular conditions found to be more prevalent in males (such as heart failure, angina and heart attack) (Gold et al., 2002). Thus, defining medical conditions in broad categories might obscure important sex differences in the prevalence of major chronic diseases that differ in terms of 'lethality'.

In the majority of studies, the approach taken to determine the 'lethality' of medical conditions was not described. It seems that in most cases, major causes of death in a generic adult population were labeled 'life-threatening' and other conditions were subsequently considered 'non-life-threatening'; however, this method is highly dependent upon disease prevalence and may not be an accurate reflection of fatal burden. Furthermore, although some common chronic conditions, such as hypertension, do not usually cause death on their own, they are also not benign conditions. Consequently, categorizing these conditions as 'non-life-threatening' may underestimate the differential impact of these conditions on male and female mortality and morbidity.

The chronic disease hypothesis also proposes that the 'non-life-threatening' nature of female chronic illnesses not only results in lower mortality, but also leads to higher morbidity. In fact, in some studies, the term 'non-life-threatening' was accompanied by other descriptors,

such as 'bothersome', 'debilitating' and 'disabling' (Crimmins et al., 2010; Newman and Brach, 2001; Verbrugge, 1984). This approach is problematic as it is an assumption that 'non-life-threatening' conditions are more 'disabling' or symptomatic than 'life-threatening' conditions. 'Life-threatening' conditions, such as cardiovascular disease, have been shown to contribute to functional impairment in older adults (Whitson et al., 2010; Newman and Brach, 2001; Kingston et al., 2014) and this impact may differ between the sexes (Whitson et al., 2010). Thus, these additional terms should not be used interchangeably with 'nonfatal' or 'non-life-threatening' when endeavoring to describe medical conditions.

3.3. Sex differences in chronic disease incidence

Cross-sectional studies of sex differences in so-called 'life-threatening' chronic conditions can distract from the fact that males and females experience similar conditions and die from similar causes. Sex differences in life expectancy can influence prevalence estimates and subsequent conclusions. For example, female longevity contributed to higher female prevalence of hypertension in three samples (Crimmins et al., 2010). This effect has not been routinely examined in studies to date. Ultimately, the key to sex differences in chronic medical conditions may lie in studies of disease incidence.

A longitudinal study found that over a two-year follow-up period, females had a lower incidence of 'fatal diseases' including heart attack, stroke and lung disease than age-matched males, but had a higher incidence of 'nonfatal' conditions including hip fracture, arthritis and cataracts (Avedano and Mackenbach, 2008). Sex differences in the incidence rate of heart disease abated after 70 years of age, which may indicate that older males are healthy survivors. On the other hand, the incidence rate of cancer plateaued in females from 60 to 69 years of age but increased in males, particularly over the age of 80 years. This result may reflect sex differences in cancer screening processes with age (Avedano and Mackenbach, 2008). Overall, this longitudinal data lends support to the original hypothesis of qualitative sex differences in chronic medical conditions and adds weight to the notion that differences in prevalence of 'life-threatening' diseases, such as heart disease and cancer, must be interpreted with caution.

3.4. Chronic disease, morbidity and mortality

The chronic disease hypothesis relates sex differences in medical conditions to sex differences in health outcomes, including mortality. Yet only a few studies have sought to determine whether sex differences in the 'lethality' of medical conditions modulate sex differences in the risk of death. In one such study, males (aged between 45 and 84 years of age) were not only more likely to have medical conditions with large effects on 2-year mortality (such as cardiovascular disease), but were also more likely to die than females with the same conditions and co-morbidity burden (Case and Paxson, 2005). Another study, which focused on adults aged 85 years and older, found that sex differences in the risk of death from 'life-threatening' diseases were impacted by the presence or absence of impairments in activities of daily living (ADLs) and mobility (Kingston et al., 2014). For example, unimpaired males faced an increased risk of death from respiratory and malignant diseases compared to unimpaired females; whereas, impaired males and females faced a similar risk of death from all diseases included in the study. If we consider impairments in ADLs and mobility to be accumulated health deficits, participants in this study varied with respect to underlying physiological reserve, or frailty. Given known differences in male and female frailty scores, it is likely to be an important confounder when examining sex differences in the 'lethality' of chronic medical conditions.

Whitson and colleagues (Whitson et al., 2010) explored the chronic disease hypothesis from a different perspective. They evaluated the relationship between sex, chronic disease and disability (defined as an impairment of one or more basic ADLs) in a sample of 5888 community-dwelling adults aged over 65 years. They found that females faced a 54% higher risk of disability than males and experienced higher prevalence of 'disabling' conditions (such as arthritis, obesity, bronchitis and vision impairment) than males. They determined that 30.2% and 12.9% of the overall sex difference in disability was mediated by the higher female prevalence of arthritis and obesity, respectively. Importantly, they also found that even though the prevalence of some medical conditions (such as stroke and coronary heart disease) was higher in males, the likelihood of disability associated with each of those conditions was significantly higher for females. Thus, this study highlighted that sex differences in disability may not be solely attributed to sex differences in disease prevalence, but fundamental differences in the disablement and recovery processes for males and females experiencing the same conditions may also play a role.

Whitson et al.'s study made a valuable contribution to our understanding of the sex paradox by evaluating the 'health' or 'morbidity' aspect of the chronic disease hypothesis. However, we would argue that defining morbidity in terms of an individual's level of disability is not sufficient to address the hypothesis because, like measures of co-morbidity, measures of disability will not identify all older adults with poor health status (Theou et al., 2012). Frailty, on the other hand, combines co-morbidity, function, mobility and other important health domains to generate a 'health gestalt' – a measure better suited to the clinically complex, older population (Cesari et al., 2016). Frailty reliably predicts risk of adverse outcomes, whether that be risk of mortality or risk of worsening morbidity, and as a result, would enable a comprehensive exploration of the chronic disease hypothesis. To date, frailty measures have not been used to explore the impact of sex differences in chronic disease on the sex paradox.

4. Acute illness and the sex-frailty paradox

Whilst chronic diseases (such as ischemic heart disease) are leading causes of death in older adults, there are acute illnesses that contribute to fatal burden. Even though sex differences in the lethality of acute illnesses may widen the male-female mortality gap, they have not been a focus of research to date. In fact, there are few studies addressing the medical condition hypothesis from an acute illness perspective.

Often cited in the literature is Verbrugge's (Verbrugge, 1984) finding that community-dwelling females aged 65 years and older experienced more acute illnesses and injuries and, as a result, more short-term disability, than males. However this study, using survey data from the 1980s, did not examine mortality as an outcome and it is not known whether a sex paradox affected this sample. Furthermore, important methodological considerations, such as the use of retrospective self-report of acute illness, may have impacted the findings via reporting and recall bias. Verbrugge (Verbrugge, 1984) also acknowledged that the survey data may have been confounded by potential sex differences in psychosocial factors, such as, healthcare utilization and illness behavior.

To minimize some of these issues, episodes of hospitalization have been used to examine sex differences in acute illness. It has been argued that hospitalization rates provide a more objective measure of acute illness incidence and morbidity because admission to hospital is dependent upon health care providers who presumably base decisions upon illness severity and need (Case and Paxson, 2005; Verbrugge, 1982). In a study of adults aged 45–84 years, males and females had equal rates of hospitalization when the prevalence of common chronic conditions were controlled (Case and Paxson, 2005). These results highlighted that there are important covariates influencing sex differences in hospitalization for acute illness. Age, functional dependency and co-morbidity burden are all likely to be important factors when considering outcomes in this population (Case and Paxson, 2005).

Admittedly, focusing on acute illnesses leading to hospitalization will underestimate overall acute illness burden in the older population.

However, it is likely to further understanding of the sex paradox by focusing on illnesses and individuals with high risk of poor outcomes. Furthermore, this context has methodological advantages, such as access to administrative datasets with standardized documentation, diagnoses formulated by trained health professionals with access to past medical history and investigation results, and (theoretically) a reduction in bias arising from psychosocial factors.

We recently examined the sex-frailty paradox in the hospitalized older adult population (Gordon et al., 2018). In our study of 1418 inpatients aged 70 years and older, female inpatients had similar levels of frailty (as measured by a 39-variable Frailty Index) as male inpatients of the same age. Evidently, this finding is not consistent with studies of community-dwelling older adults. We hypothesized that older inpatients represent a more homogeneous subset of the geriatric population and sex differences in frailty may not be present prior to onset of acute illness and hospitalization in this group. Alternatively, female inpatients may have higher baseline frailty scores than males and sex differences in the nature of severity of illness may close the male-female frailty gap. Despite similar frailty scores, female inpatients faced a significantly lower risk of 28-day mortality than males of the same age and frailty (Gordon et al., 2018). Whilst male inpatients were more likely to be admitted with an acute condition carrying a high-risk of 28-day mortality (such as, sepsis, pneumonia, stroke and congestive cardiac failure), this did not close the sex-mortality gap in this study.

Sex differences in disease severity and complexity as well as other (potential) confounding factors may provide alternative explanations for the study results. In acute illness, there is some evidence that older male inpatients score higher than female inpatients on physiological severity tools (Rozzini et al., 2009). However, female inpatients appear to still have a lower risk of mortality than male inpatients matched for physiological derangement, age and frailty (Romero-Ortuno et al., 2016). In a study of chronic cardiovascular disease, noninvasive measures of vascular disease (such as carotid artery ultrasound and echocardiography) demonstrated more extensive disease in males compared with females of the same age (Fried et al., 1998). However, sex differences in the severity of cardiovascular disease did not completely explain the sex-mortality gap in that study since males were still more likely to die than females, even when matched for age and burden of subclinical disease (Fried et al., 1998).

5. Conclusion

This review summarized current knowledge of biological, behavioral and social explanations for sex differences in morbidity, mortality and frailty and highlighted the issue at the center of the sex paradox – that females are more tolerant of frailty than males. Our evaluation of the frequently cited ‘chronic disease hypothesis’ (that males experience more ‘life-threatening’ diseases whereas females experience more ‘non-life-threatening’ and ‘disabling’ diseases) demonstrated significant between-study methodological differences. As a result, there is a lack of convincing evidence to confirm (or refute) this hypothesis at this point in time. Frailty should be considered to be an important covariate and outcome variable in future studies. This useful construct provides an opportunity to investigate the sex paradox in a systematic way, leading to a better understanding of aging and disease as well as the development of effective, sex-specific management and prevention strategies.

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